Sildenafil: a Revolutionary Therapy?

Introduction

Erectile dysfunction is a common, underestimated problem in diabetes, the reported prevalence ranging from 2–85 % and increasing with increasing duration of diabetes and with age.[1–3] The aetiology is multifactorial, one series reporting evidence of vascular disease alone in 38 %, autonomic neuropathy alone in 23 % and vascular plus neuropathic changes in 35 %.[4] Psychological problems, in isolation or in combination with physical causes, must not be forgotten. Much less is know about sexual dysfunction in women with diabetes.[5] Until recently, available treatments have been intrusive and not widely accepted. The prospect of a novel oral agent, sildenafil, which only acts when the person is sexually aroused, has generated a great deal of publicity, interest and expectation.

Mechanism of Action of Sildenafil

Sildenafil acts by inhibiting the breakdown of cyclic guanosine monophosphate (cGMP) by a specific type 5 cGMP phosphodiesterase.[6] It is thus only effective when nitric oxide (NO) and thus cGMP production in penile tissue is increased by central or reflex arousal. In addition, NO and cGMP are synthesized in other tissues and involved in other signalling pathways, so that sildenafil potentially may have widespread effects.

Effectiveness of Sildenafil

The first reported study concerned 12 non-diabetic subjects, aged 36–63 years, with no established organic cause for erectile dysfunction. A single dose of oral sildenafil 10–50 mg produced greater penile rigidity, measured objectively, than placebo with visual sexual stimulation, in a dose-dependent fashion.[7] During treatment with sildenafil 25 mg daily for 7 days, the number of erections in the 2 h after dosing was greater than on placebo treatment.

In a double-blind, placebo-controlled, fixed-dose study for 24 weeks, of 532 men with organic, psychogenic or mixed causes for erectile dysfunction, increasing doses of sildenafil (25, 50 or 100 mg) increased the frequency of penetration and maintenance of erection after penetration.[8] A second group of 329 men were randomly assigned to take placebo or sildenafil 50 mg for 12 weeks. The dose could be increased or decreased by 50 % on the basis of the therapeutic response or adverse effects. At the end of the study, the proportions of men taking 25, 50 or 100 mg sildenafil were 2, 23 and 74 %. Again, frequency of penetration and maintenance of erection after penetration were significantly increased with active treatment. Mean scores for a number of sexual functions were significantly increased on active treatment, whereas sexual desire was unchanged. 69 % of all attempts at sexual intercourse by men receiving sildenafil were successful in the last four weeks of treatment, as compared with 22 % of those receiving placebo. Approximately 10 % of these men had diabetes but responses in these men were not analyzed separately.

In a placebo-controlled study of 21 men with diabetes, aged 42–65 years, a single dose of sildenafil 25 or 50 mg significantly increased penile rigidity in response to visual sexual stimulation.[9] During treatment with 25 or 50 mg daily for 10 days, the number of erections enabling penetration increased significantly. Improved erections were reported by 50 and 52% of men taking 25 and 50 mg sildenafil respectively, compared to 10 % of those receiving placebo. In another large, placebo-controlled study, so far only reported in abstract, diabetic men with erectile dysfunction, mean age 57 years, were randomized to receive placebo or sildenafil 25–100 mg for 12 weeks.[10] Men receiving active drug therapy had higher scores for frequency of penetration and maintenance of erection after penetration. Improved erections were reported by 57 % of those receiving sildenafil compared to 10 % of those taking placebo.

Thus the drug improves sexual function in 50–60 % of men with diabetes. However, it is likely that men who have not responded to other therapies, who presumably have severe vascular disease, will also not respond to sildenafil. No data have yet been published in women.

Safety

In the above trials, the drug was apparently generally well tolerated, headache, dyspepsia, flushing and visual disturbance being the commonly reported problems.[11] The drop-out rate was small and no major adverse events, including priapism, were reported. However, in at least one study,[9] men with clinically significant ischaemic heart disease and peripheral vascular disease were excluded. If taken along with any organic nitrate, a precipitous fall in systemic blood pressure may occur. Sildenafil therefore must not be prescribed for men taking a nitrate for medical or recreational purposes.

The drug has been available in the USA since late March 1998. During post-marketing surveillance by the US Food and Drug Administration (FDA) to the end of July 1998, when more than 3.6 million prescriptions for the drug had been dispensed, 123 deaths were reported in individuals who had been prescribed the drug.[12] Of

* Correspondence to: Dr SM Marshall, Department of Medicine, The Medical School, Framlington Place, Newcastle upon Tyne, NE2 4HH, UK

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the 69 US citizens (66 men), median age 64 years (range 29–87 years), the cause of death was unknown in 21, 2 had strokes and 46 cardiac events. Where the dose was specified (in 31), 26 had taken 50 mg, 3 100 mg and 2 50–100 mg. Twelve had also been prescribed a nitrate medication. Of the reports which provided information on sexual activity, 18 men died or developed symptoms that lead to death during or immediately after sexual activity and 25 within 4–5 h. Fifty-one patients (74 %) had one or more risk factor for coronary artery disease, including diabetes. Three additional subjects without known heart disease or risk factors had severe coronary artery disease at post mortem.

The reporting of the above deaths is voluntary and the magnitude of underreporting unknown. It is thus not possible to calculate true incidence rates for fatalities nor to determine the role of the drug, if any, in the deaths. Many of the men had known risk factors for coronary heart disease, as will many men with diabetes, so that they may have been at risk during sexual activity anyway. Diabetic men with erectile dysfunction are more likely to have ischaemic heart disease[2] and in addition, silent myocardial ischaemia is more likely in people with diabetes.[13]

Conclusions and Recommendations

Oral sildenafil is a well-tolerated and effective agent for managing erectile dysfunction, improvement occurring in 50–60 % of diabetic men, a response rate similar to that for transurethral administration of alprostadil.[14] However, because of its oral administration, sildenafil is likely to become first-line therapy. Data concerning the drug's safety in people with macrovascular disease or its risk factors is currently limited but caution is advisable. Treatment is probably best avoided in men with severe angina or left ventricular dysfunction. There is no current indication to prescribe the drug for men with normal sexual function or for women.

All diabetic men with erectile dysfunction who wish to be considered for treatment should have a thorough medical assessment and should discuss the potential benefits and risks associated with therapy. This assessment is best done by the designated lead physician responsible for the person's diabetes care, whether in primary or secondary care. A suggested approach is shown in Table 1. Much of this information will be readily available from the diabetes annual review. Objective diagnosis of erectile dysfunction is not practicable in all men, but futher specialist investigation may be useful in younger men of short duration diabetes without microvascular or macrovascular complications.

The 50–60 % chance of benefit should be discussed to allow realistic expectation and possible alternative treatments mentioned. Warning of the common side-effects of dyspepsia, headache, flushing and visual disturbance must be given along with instructions on what to do in the unlikely event of priapism. The possibility of a more serious adverse event is worthy of mention to all men, and in those with known macrovascular disease, the potential risks of sexual activity and treatment carefully discussed. The importance of not taking any form of nitrate, including recreational drugs, must be stressed. The current recommended starting dose is 50 mg, to be taken no more than once a day, one hour before sexual activity, with no other treatment for impotence at the same time.

Table 1. A suggested approach to the assessment of a diabetic man with erectile dysfunction

Identify a likely cause of erectile dysfunction: exclude a specifically treatable cause	
Hormonal:	FSH/LH; testosterone, SHBG; prolactin; thyroid function
Vascular:	history of macrovascular disease
Neuropathic:	evidence of peripheral/autonomic neuropathy
Exclude a local anatomical abnormality	
	physical examination
Drug history	
	drugs which might exacerbate erectile dysfunction
	drugs which would exclude prescription of sildenafil (nitrates)
Assessment of cardiovascular risk	
	known large vessel disease
	macrovascular risk factors

SHBG: sex hormone binding globulin.

Further information is obtainable online from a number of sources: FDA,[11] the drug manufacturers (http://www.viagra.com), the Pillbox pharmacy (http://www.thepillbox.com/viagra.phtml) and Viagra Talk (http://www.bigv.com/).

SM Marshall
Department of Medicine,
The Medical School,
Framlington Place, Newcastle
upon Tyne, NE2 4HH, UK

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Ms Catriona Hauer
Journal Customer Services
Blackwell Science Ltd
Osney Mead
Oxford
United Kingdom
OX2 0EL

Tel: +44 1865 206125
Fax: +44 1865 206219
E-mail: catriona.hauer@blacksci.co.uk

